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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,114	03/23/2004	Victor Lyamichev	FORS-08793	2778

72960 7590 07/22/2008

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
07/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,114	LYAMICHEV ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 11, 2007 has been entered.

2. All previous grounds of rejection are withdrawn in view of the amendment to cancel claims 66-72 and add new claims 73-82. This action contains new grounds of rejection as set forth below.

Election/Restrictions

3. Applicant's election of Group I, SEQ ID NO: 167 and the oligonucleotide that hybridizes to a region comprising nucleotides 1394-1396 of SEQ ID NO: 158 in the reply filed on April 15, 2008 and April 28, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 73-82 are pending and have been examined herein.

Claim Objections

5. Claims 75-82 are objected to because of the following informalities:

In claims 75-82 "iii" and "iv" should read "i" and "ii" (see claim 75, lines 3 and 5).

Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112 – New Matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the subject matter of newly added claims 75-82. While the originally filed specification discloses methods for detecting HIV by contacting a sample with an oligonucleotide, the originally filed specification does not appear to provide support for the concept of a method wherein a sample is contacted with any oligonucleotide wherein at least a portion of the oligonucleotide hybridizes with a region of an HIV target sequence comprising nucleotides 1394-1396 of SEQ ID NO: 158. In Figure 55C, a "primer 8" is disclosed which includes nucleotides 1394-1396 of SEQ ID NO: 158 , i.e., 5'-ACAGCAUGUCAGGGAGU**AGG** -3'. Thereby, the specification provides support for a method of detecting HIV by contacting a sample with an oligonucleotide comprising 5'-ACAGCAUGUCAGGGAGUAGG – 3'. However, this disclosure does not provide support for the broader concept of methods which use any oligonucleotide that

hybridizes to any target sequence that includes an "AGG," as is encompassed by the present claims. Further, regarding claims 75-82, the specification does not appear to provide support for the recitation of a method wherein said oligonucleotide that hybridizes to a target region comprising an AGG is an antisense oligonucleotide. While the specification teaches the general concept of antisense nucleic acids, these general teachings do not provide support for the concept of a method wherein the antisense oligonucleotide is the particular subgenus of oligonucleotides that hybridize to a region of HIV that comprise the AGG of nucleotides 1394-1396 of SEQ ID NO: 158. Additionally, regarding claim 82, while the specification teaches the general concept of methods of exposing a sample to an antisense oligonucleotide, wherein exposing results in the inhibition of expression of an HIV target sequence, this general teaching does not provide support for the specifically claimed subject matter of a method comprising exposing a sample to any antisense oligonucleotide that hybridizes to a region of HIV that includes the AGG nucleotides of nucleotides 1394-1396 of SEQ ID NO: 158, wherein said exposing results in inhibition of one or more genes from an HIV target sequence.

In the reply of October 11, 2007, Applicants state that the newly added claims are the same as those that were filed as claims 50-65 in the preliminary amendment of March 23, 2004 and thereby are not new matter. However, the present application is a divisional of US Application No. 09/882,945. The subject matter of claims 75-82 was not presented in the originally filed claims of '945 and does not appear to have support in the specification of the '945 application. Applicants do not point to any particular

teachings in the originally filed specification as providing support for the subject matter of newly added claims 75-82.

Claim Rejections - 35 USC § 112 second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps required to detect the presence of HIV. The claims are drawn to methods for detecting HIV and include the steps of providing a sample and an oligonucleotide, exposing the sample to the oligonucleotide and detecting the presence of HIV. The claims omit the essential steps which allow for the detection of HIV - e.g., by detecting hybridization of the oligonucleotide to a target nucleic acid, wherein the occurrence of hybridization of the oligonucleotide to the target nucleic acid is indicative of the presence of HIV. As written, it is unclear as to the relevance of the exposing step and it is unclear as to what step or element allows for the detection of HIV.

Claim Rejections - 35 USC § 112 - Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting the presence of a target HIV nucleic acid sequence comprising: i) isolating a nucleic acid sample from a human subject; ii) contacting the nucleic acid sample with an oligonucleotide consisting of SEQ ID NO: 167; and iii) and detecting hybridization of said oligonucleotide to target nucleic acids present in the nucleic acid sample as indicative of the presence of a target HIV nucleic acid sequence, does not reasonably provide enablement for in vivo methods for detecting HIV target sequences, in vivo methods wherein exposing a sample to an oligonucleotide results in inhibiting expression of a target nucleotide sequence, or methods of exposing a sample to any oligonucleotide that hybridizes to any sequence that comprises nucleotides 1394-1396 of SEQ ID NO: 158 (i.e., the sequence AGG), wherein said exposing results in the detection of a HIV target nucleic acid or results in inhibiting expression of a target HIV nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 73-74 are drawn to methods for detecting the presence of HIV comprising providing a sample suspected of containing HIV and an oligonucleotide, exposing the sample to the oligonucleotide, and detecting the presence of HIV. The claims do not require isolating a sample from a subject. Rather, the claims broadly recite "providing a sample." In view of the teachings and the claims as originally filed in parent application 09/882,945, “providing a sample" appears to include providing a cell that is present in a human or non-human animal subject. Accordingly, claims 73-74 read on in vivo methods for detecting HIV.

Claims 75-82 are directed to methods comprising providing a sample suspected of containing or known to contain HIV target sequences and an oligonucleotide that hybridizes to a region of an HIV target region that comprises nucleotides 1394-1396 of SEQ ID NO: 158, and exposing the sample to the oligonucleotide. As discussed above, in view of the “providing a sample” language, the claims appear to include in vivo methods for detecting HIV. Claims 80-82 further recite that the oligonucleotide is an antisense oligonucleotide and that the exposing step results in inhibition of one or more genes from said HIV target sequence. Accordingly, these claims read on in vivo methods in humans and animals in which exposure to an oligonucleotide results in inhibition of expression. Additionally, claims 75-82 broadly define the oligonucleotide only in terms of the fact that it hybridizes to the three nucleotides of nucleotides 1394-1396 of SEQ ID NO: 158 - i.e., an AGG. The claims do not define the overall structure of the oligonucleotide – e.g., its length, its full sequence, the particular sequence that

the full length oligonucleotide hybridizes to, or the conditions of hybridization. Thereby, the claims encompass the use of a significantly broad genus of oligonucleotides in which any number of nucleotides of any identity are added to a 5'-CCT-3' fragment.

Nature of the Invention:

The claims are drawn to methods for detecting HIV using an oligonucleotide. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F. 3d 1316, 1330 (Fed Cir. 2001).

Teachings in the Specification and State of the Art:

The specification teaches a nucleic acid consisting of nucleotides 455-2076 of the HIV gag gene – i.e., SEQ ID NO: 158.

The specification (Figure 55C)also teaches a primer referred to therein as "primer 8" which consists of nucleotides 5'-ACAGCAUGUAGGGAGUAGG-3'. This primer includes the 3' nucleotides 1394-1396 of SEQ ID NO: 158 - i.e., **AGG**. The specification teaches another primer that hybridizes to the region including nucleotides 1394-1396 – that is, the primer of SEQ ID NO: 190, consisting of nucleotides 5'-AGGGAGTAGGAGGAGG-3'. An INVADER assay is described in which SEQ ID NO: 190 is used in combination with SEQ ID NO: 189 and 180 to detect HIV target nucleic acids (Figure 59, page 60.

The specification further teaches the oligonucleotide of SEQ ID NO: 167 – 5'-AAAACTCCTACTCCC-3'. In Figure 57, SEQ ID NO: 167 is described as including the sequence CTCCTACTCCC, which is complementary to sequences within SEQ ID

NO: 158, including nucleotides 1394-1396 of SEQ ID NO: 158, and further including at it's 5' terminus the sequence "AAAA." The specification (page 59) characterizes SEQ ID NO: 167 as a signal probe used in the INVADER assay.

Additionally, the prior art of Agrawal (U.S. Patent No. 7,173,014) discloses antisense oligonucleotides consisting of the sequences of SEQ ID NO: 1-4 therein, wherein the sequences are complementary to a region of the HIV gag gene that includes an 5-AGG-3' (see Table 2 therein). However, the present specification does not contemplate methods which detect the specific oligonucleotides of Agrawal. Accordingly, the specification cannot be relied upon for providing support or enablement for methods of exposing a sample to the oligonucleotides of SEQ ID NO: 1-4 of Agrawal.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

As discussed above, the claims encompass in vivo methods of exposing a sample (such as a cell present in a human or non-human animal) with an oligonucleotide, and then detecting hybridization of the oligonucleotide with a target nucleic acid. The claims also include methods in which the exposing a sample to an oligonucleotide results in inhibition of expression of any one or more HIV target genes. However, in vivo administration of oligonucleotides is unpredictable because the success of such administration is dependent on adequate concentrations of the oligonucleotide reaching the desired site in vivo, hybridizing the oligonucleotide to a specific gene sequence, and inhibiting expression of a target gene. Specifically, in vivo administration of oligonucleotides is unpredictable for the following reasons: (i) The

oligonucleotides may be degraded in blood and tissues under physiological conditions and therefore may not reach the target site in sufficient quantities to induce recombination; (ii) The ability of the oligonucleotide to be taken up by the cell is expected to be different under physiological conditions as versus tissue culture, i.e. the permeability of the cell would be different under physiological conditions and would be expected to vary with cell type; (iii) It is not clear what would be the optimum concentration of the oligonucleotide required for effective treatment, the mode of administration and the pharmacokinetics of therapy for the oligonucleotide; and (iv) The ability of the oligonucleotide to form a stable hybridization complex under physiological conditions is unpredictable since the formation of the hybridization complex varies significantly with oligonucleotide length, and chemical composition and is highly affected by the presence of secondary and tertiary nucleic acid structures. Therefore, for each oligonucleotide, one must develop de novo the appropriate set of parameters for in vivo function. While the specification provides a general discussion regarding the use of antisense oligonucleotides, there is insufficient guidance provided in the specification as to how to use any particular oligonucleotides for therapeutic or diagnostic purposes in vivo and therefore one is left to develop de novo the appropriate techniques for selection, delivery and effective use of each oligonucleotide.

In view of the unpredictability in the art of oligonucleotide therapeutics, the skilled artisan would not accept that results obtained in vitro are reasonably predictive of the results obtained in vivo for because the correlation between in vitro and in vivo results is not a general characteristic that can be applied to each and every oligonucleotide and

the record has not established a universal correlation between the results obtained in vitro with HIV oligonucleotides/donor and the results obtained in vivo.

Moreover, for oligonucleotides that are defined only in terms of the fact that they hybridize with a 3 nucleotide region (i.e., nucleotides AGG), the ability to use such oligonucleotides to inhibit expression of a target sequence is further unpredictable because there is no means to predict a priori where in the human or non-human animal genome such oligonucleotides will hybridize, in addition to hybridizing to sequences in the HIV genome. In order to effectively inhibit expression of a target nucleic acid, an oligonucleotide must hybridize with specificity to the target nucleic acid and with sufficient stability to inhibit the expression of the target nucleic acid. Extensive experimentation would be required to determine which oligonucleotides of 3, 4, 5 etc nucleotides hybridize with sufficient specificity and stability to HIV target nucleic acids in order to effectively inhibit the expression of the target nucleic acid.

Amount of Direction or Guidance Provided by the Specification:

Regarding claims 73 and 74, the specification does not provide any particular guidance as to how to use nucleic acids comprising SEQ ID NO: 167 to detect HIV. The specification does not teach that this sequence is present in HIV or complementary to a sequence present in HIV. While portions of the 3' region of SEQ ID NO: 167 are complementary to HIV gag sequences, the 5' portion of SEQ ID NO: 167 does not appear to be complementary to HIV gag sequences. The claims require only a step of exposing a sample to SEQ ID NO: 167 and then detecting HIV. The claims and specification do not provide any details or guidance as to how the use of a nucleic acid

that does not share complementarity with the 5' region of HIV can be used alone to detect HIV target sequences.

Regarding in vivo administration of oligonucleotides, the specification does not provide any particular guidance as to how to use oligonucleotides that comprise SEQ ID NO: 167 or oligonucleotides that are complementary to AGG to detect HIV in vivo. The specification also does not provide any particular guidance as to how to use oligonucleotides that are complementary to AGG to inhibit expression of any HIV target gene. At the time the invention was made, it was well recognized in the art that significant experimentation would be required to practice the in vivo administration of oligonucleotides. Yet, the specification provides only general guidelines for generating and using oligonucleotides in vivo, leaving the artisan to develop de novo the appropriate techniques for in vivo delivery and effective use of oligonucleotides to detect HIV target sequences in vivo or to inhibit expression of HIV target sequences in vivo.

Further, the specification does not provide any specific guidance as to how to select particular oligonucleotides to effectively inhibit the expression of one or more HIV target nucleic acids. There is no particular guidance provided in the specification regarding the length of the oligonucleotides or the full structure of the HIV sequence to which the oligonucleotide should hybridize in order to effectively inhibit expression of the HIV gag gene or other HIV gene sequences.

Working Examples:

The specification teaches the gag sequences of HIV (i.e., SEQ ID NO: 158) and exemplifies in vitro methods for detecting HIV gag target nucleic acids in an INVADER assay using the oligonucleotide consisting of SEQ ID NO: 167.

The specification does not exemplify any methods wherein SEQ ID NO: 167 or an oligonucleotide that hybridizes to nucleotides 1394-1396 (i.e., AGG) of SEQ ID NO: 158 is used in vivo to detect the presence of HIV target sequences.

The specification also does not exemplify any methods wherein a sample is exposed, in vivo or in vitro, to an oligonucleotide that hybridizes to nucleotides 1394-1396 (i.e., AGG) of SEQ ID NO: 158, wherein the exposing results in the inhibition of expression of any one or more HIV target sequences.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification does not teach

or provide sufficient guidance as to how to use any oligonucleotide that hybridizes to an AGG sequence to inhibit expression of any HIV target nucleic acid. Further, the specification does not provide sufficient guidance as to how to perform in vivo methods of exposing a sample to an oligonucleotide comprising SEQ ID NO :167 or an oligonucleotide that hybridizes to an AGG sequence, wherein said exposing results in the detection of HIV target sequences or the inhibition of HIV target sequences. Although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and in view of the unpredictability in the art, it would require undue experimentation for one of skill in the art to make and use the broadly claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 75 and 80-82 are rejected under 35 U.S.C. 102(e) as being anticipated by Agrawal (U.S. Patent No. 7,173,014).

The present claims are drawn to methods comprising providing a sample suspected of containing HIV and an oligonucleotide that hybridizes to a region of HIV that comprises nucleotides 1394-1396 of SEQ ID NO: 158, and exposing the sample to

the oligonucleotide. Since nucleotides 1394-1396 consist of an AGG, the claims encompass exposing a sample to an oligonucleotide that hybridizes to any sequence comprising an AGG.

Agrawal (col. 2, lines 48-63; col. 4, lines 1-19) teaches methods of exposing a sample suspected of containing HIV target nucleic acids with an antisense oligonucleotide, wherein the antisense oligonucleotide consists of a nucleotide sequence complementary to gag conserved nucleotide sequences. In particular, Agrawal teaches methods of exposing a sample to the oligonucleotide of SEQ ID NO: 1 therein (col. 3, lines 46-50). SEQ ID NO: 1 consists of the sequence: 5'-UCGCACCATCTCTCTCCUUC-3' (see Table 2). Thereby, the oligonucleotide of SEQ ID NO: 1 of Agrawal hybridizes to a region of HIV that comprises an 5'-AGG – 3':

5'-UCGCACCATCTCTCTCCUUC-3'
3'-GGA-5'

Agrawal also teaches methods which comprise exposing a sample to the oligonucleotides of SEQ ID NO: 2-4 therein, wherein each of these oligonucleotides also comprise the sequence 5-CCU-3' or 5'CCT-3', and thereby hybridize to a region comprising 5'-AGG-3' (see Table 2).

Regarding claims 80 and 81, the oligonucleotides of Agrawal are single-stranded antisense oligonucleotides (col. 5, lines 4-22, and Table 2).

Regarding claim 82, Agrawal teaches that exposing cells to the oligonucleotides of SEQ ID NO: 1-4 results in inhibition of expression of HIV gag sequences (col. 12 and 16-17).

10. Claims 75-77, 80 and 81 are rejected under 35 U.S.C. 102(e) as being anticipated by Irvine (U.S. Patent No. 6,300,056).

The present claims are drawn to methods comprising providing a sample suspected of containing HIV and an oligonucleotide that hybridizes to a region of HIV that comprises nucleotides 1394-1396 of SEQ ID NO: 158, and exposing the sample to the oligonucleotide. Since nucleotides 1394-1396 consist of an AGG, the claims encompass exposing a sample to an oligonucleotide that hybridizes to any sequence comprising an AGG.

Irvine (col. 14) teaches a method for detecting HIV target nucleic acids comprising providing a sample and an oligonucleotide probe, and exposing the sample to the probe, wherein said exposing results in hybridization between sample target nucleic acids and the probe and hybridization is detected as indicative of the presence of HIV target nucleic acids. Irvine (col. 15-16) teaches a number of probes that are complementary to HIV gag and pol nucleic acid sequences. For example, Irvine teaches a probe (referred to therein as SEQ ID NO: 47; col. 15) that is complementary to a conserved HIV gag sequence, wherein the probe comprises:
5'- TATTCCTAAYTGRACTTCCCARAARTCYTGAGT -3' (see Sequence Listing therein). Thereby, the oligonucleotide of SEQ ID NO: 1 of Irvine hybridizes to a region of HIV that comprises an 5'-AGG – 3':

5'- TATTCCTAAYTGRACTTCCCARAARTCYTGAGT -3'
3'-**GGA**-5'

Regarding claims 80 and 81, the probes of Irvine are the inverse complements of HIV target nucleic acids and consist of a single-strand of nucleic acid and thereby are

considered to be "antisense oligonucleotides." Accordingly, the method of Irvine anticipates the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Irvine in view of Kaiser et al (WO 98/23774, June 4, 1998).

The teachings of Irvine are presented above. In particular, Irvine teaches hybridization methods for detecting HIV target nucleic acids comprising exposing a target nucleic acid to an oligonucleotide probe. Irvine does not teach methods wherein the exposing comprises an invasive cleavage assay.

However, Kaiser teaches methods for detecting target nucleic acids using an invader-directed cleavage reaction (e.g., page 146). Kaiser teaches that this method can be used to specifically detect the presence of HIV target nucleic acid sequences (page 151). Kaiser also teaches that the INVADER-directed cleavage reaction provides "an ideal direct detection method that combines the advantages of the direct detection assays (e.g., easy quantification and minimal risk of carry-over contamination) with the specificity provided by a dual or tri oligonucleotide hybridization assay (see page 217).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Irvine so as to have used the HIV probe disclosed therein in an INVADER cleavage assay in order to have provided the advantages set forth by Kaiser of providing an easy quantitative method, having a minimal risk of carry-over contamination and a high level of specificity of detection.

12. Claims 73-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaiser et al (WO 98/23774) in view of Irvine (U.S. Patent No. 6,300,056), Korber et al (Human Retroviruses and AIDS. 1998), and Hogan (US Pat. 5,541,308, July 30, 1996).

Kaiser teaches methods for detecting target nucleic acids using an invader-directed cleavage reaction, wherein the methods comprise providing a sample comprising target nucleic acid and a set of oligonucleotides, exposing the sample to the oligonucleotides, and detecting hybridization of the oligonucleotides with nucleic acids as indicative of the presence of a specific target nucleic acid (e.g., page 146). Kaiser

teaches that this method can be used to specifically detect the presence of HIV target nucleic acid sequences in a biological sample (page 151).

The reference provides extensive guidance as to how to select oligonucleotides that are complementary to particular sequences in the target nucleic acid, such that the oligonucleotides have an optimum length, melting temperature and specificity (pages 55-60 and 66). Kaiser (pages 90-91, 216, Figure 127) further teaches structure specific cleavage assays wherein a 5' tag of 4 nucleotides (e.g., "TTTT") and a fluorescein label are added to the 5' terminus of a probe. The 3' region of the probe comprises nucleotides that are complementary to the target nucleic acid sequence. Hybridization of the probe to the target nucleic results in a cleavage reaction wherein the 5' terminal nucleotides and the fluorescein label are released and detected as indicative of the presence of the target nucleic acid. Kaiser also teaches that alternative 5' tags may be used such as poly A sequences (e.g., page 79).

Kaiser concludes that the INVADER-directed cleavage reaction provides "an ideal direct detection method that combines the advantages of the direct detection assays (e.g., easy quantification and minimal risk of carry-over contamination) with the specificity provided by a dual or tri oligonucleotide hybridization assay (see page 217).

Kaiser does not specifically teach a method for detecting HIV target nucleic acids wherein the oligonucleotide comprises SEQ ID NO: 167 or the oligonucleotide is complementary to nucleotides 1394-1396 (i.e., AGG) of SEQ ID NO: 158.

However, present SEQ ID NO: 167 constitutes a sequence of the HIV gag gene. Sequences of the HIV gag gene, as well as probes for detecting HIV gag gene

sequences were well known in the art at the time the invention was made. In particular, Irvine (col. 14) teaches a method for detecting HIV target nucleic acids comprising providing a sample and an oligonucleotide probe, and exposing the sample to the probe, wherein said exposing results in hybridization between sample target nucleic acids and the probe and hybridization is detected as indicative of the presence of HIV target nucleic acids. Irvine (col. 15-16) teaches a number of probes that are complementary to HIV gag and pol nucleic acid sequences.

Korber et al (i.e., the Human Retrovirus and AIDS 1998 Compendium database) provides a comparison of sequences of the HIV-1 gag gene from a significantly large number of different HIV-1 isolates, as well as a comparison of the HIV-1 gag sequences with HIV-2 and SIV gag sequences. A comparison of the HIV gag sequences provided in the database identifies sequences that are conserved between HIV isolates, and which can therefore be used to simultaneously detect the largest number of HIV isolates.

Further, extensive guidance is provided in the prior art as to how to make and use primers that detect multiple variants of a virus, or which are specific for one variant of a virus. Designing probes which are equivalents to those taught in the art requires only routine experimentation. The parameters and objectives involved in the selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is

replete with guidance and information necessary to permit the ordinary artisan to design additional probes for the detection of HIV.

For example, Hogan (col. 6, line 65 to col. 7, line 29) provides extensive guidance for the selection of oligonucleotide primers and probes,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{o}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (column 10, lines 13-15).

Given that the prior art of Korber provides a database of the sequences of the gag gene of a multitude of HIV isolates, as well as gag gene sequences from HIV-2 and SIV, and the prior art of Irvine specifically provides the motivation to obtain probes

complementary to HIV gag sequences, and given that the prior art provides extensive guidance as to how to select additional probes to sequences common to HIV-1 isolates, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional probes to detect HIV, include probes that comprise nucleotides CTCCTACTCCC of SEQ ID NO: 167, as well as probes which are complementary to the region of nucleotides 1394-1396 (AGG) of SEQ ID NO: 158. Given the extensive guidance provided in the prior art, the ordinary artisan would have had more than a reasonable expectation of success of generating additional probes for the detection of HIV, including the presently claimed probes. Additionally, in view of the teachings of Kaiser of adding a 5' tag sequence to the probe that is cleavable in a structure specific cleavage assay and the guidance provided by Kaiser for generating such 5' tags, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have added a 5' tag, including an "AAAA" tag to the HIV gag probe, including a probe comprising CTCCTACTCCC, in order to have provided a probe that could be used in the structure specific cleavage assays of Kaiser. Additionally, the ordinary artisan would have been motivated to have modified the method of Kaiser so as to have contacted the sample suspected of containing HIV with HIV gag probes, and particularly with a probes comprising SEQ ID NO: 167 or a probe complementary to a sequence comprising AGG, in order to have provided an invasive cleavage assay that could be used to easily and rapidly detect HIV target nucleic acids in a biological sample with a high level of specificity of detection.

Regarding claims 80 and 81, the generated HIV gag probes consisting of the inverse complements of HIV target nucleic acids and consisting of a single-strand of nucleic acid have the property of being "antisense oligonucleotides."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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